

SARS-CoV-2 Vaccination Safety in Guillain-Barré Syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, and Multifocal Motor Neuropathy

Adája E. Baars, MD, Krista Kuitwaard, MD, PhD, Laura C. de Koning, BSc, Linda W.G. Luijten, MD, W. Maaïke Kok, BSc, Filip Eftimov, MD, PhD, Luuk Wieske, MD, PhD, H. Stephan Goedee, MD, PhD, W. Ludo van der Pol, MD, PhD, Patricia H. Blomkwist-Markens, Anja M.C. Horemans, MD, PhD, Bart C. Jacobs, MD, PhD, and Pieter A. van Doorn, MD, PhD

Correspondence

Dr. van Doorn
p.a.vandoorn@
erasmusmc.nl

Neurology® 2023;100:e182-e191. doi:10.1212/WNL.0000000000201376

Abstract

Background and Objectives

There are concerns on the safety of SARS-CoV-2 vaccination in patients with a history of Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN). The aim of this study was to determine the risk of recurrence of GBS and exacerbations of CIDP or MMN after SARS-CoV-2 vaccination.

Methods

We conducted a prospective, multicenter cohort study from January 2021 to August 2021. Patients known in 1 of 3 Dutch University Medical Centers with research focus on immune-mediated neuropathy and members of the Dutch Patient Association for Neuromuscular Diseases were invited to participate if they were 18 years or older and diagnosed with GBS, CIDP, or MMN. Participants completed a series of questionnaires at 4 different time points: study baseline (1), within 48 hours before any SARS-CoV-2 vaccination (2 and 3, if applicable), and 6 weeks after their last vaccination (4). Participants unwilling to get vaccinated completed the last questionnaire (4) 4 months after study baseline. We assessed recurrences of GBS, any worsening of CIDP or MMN-related symptoms, treatment alterations, and hospitalization.

Results

Of 1,152 individuals to whom we sent the questionnaires, 674 (59%) signed informed consent. We excluded 153 individuals, most often because they had already received a SARS-CoV-2 vaccination or had had the infection (84%) before study baseline. Of 521 participants included in analyses, 403 (81%) completed the last questionnaire (time point 4). None of 162 participants with a history of GBS had a recurrence after vaccination. Of 188 participants with CIDP, 10 participants (5%) reported a worsening of symptoms within 6 weeks after vaccination. In 5 (3%) of these patients, maintenance treatment was modified. Two of 53 participants with MMN (4%) reported a worsening of symptoms, and treatment modification was reported by 1 participant.

Discussion

We found no increased risk of GBS recurrence and a low to negligible risk of worsening of CIDP or MMN-related symptoms after SARS-CoV-2 vaccination. Based on our data, SARS-CoV-2 vaccination in patients with these immune-mediated neuropathies seems to be safe.

RELATED ARTICLE

Editorial

SARS-CoV-2 Vaccination and Autoimmune Neuropathies: Rebalancing the Risk

Page 55

MORE ONLINE

COVID-19 Resources

For the latest articles, invited commentaries, and blogs from physicians around the world

[NPub.org/COVID19](https://www.neurology.org/COVID19)

From the Department of Neurology (A.E.B., K.K., L.C.K., L.W.G.L., W.M.K., B.C.J., P.A.D.), Erasmus MC University Medical Center, Rotterdam; Department of Neurology (K.K.), Albert Schweitzer Hospital, Dordrecht; Department of Neurology (L.W.G.L.), St. Elisabeth-TweeSteden Hospital, Tilburg; Department of Neurology (F.E., L.W.), Amsterdam University Medical Center, University of Amsterdam; Department of Neurology and Neurosurgery (H.S.G., W.L.P.), Brain Center University Medical Center Utrecht; Dutch Patient Organization for Neuromuscular Diseases (P.H.B.-M., A.M.C.H.), Baarn; and Department of Immunology (B.C.J.), Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CIDP = chronic inflammatory demyelinating polyneuropathy; **GBS** = Guillain-Barré syndrome; **IVIg** = intravenous immunoglobulins; **MMN** = multifocal motor neuropathy.

The introduction of SARS-CoV-2 vaccinations is an important milestone in the COVID-19 pandemic. However, patients with a history of an immune-mediated neuropathy are often concerned about the safety of vaccinations because of a possible recurrence of Guillain-Barré syndrome (GBS) or exacerbations of chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy (MMN).^{1,2}

GBS usually is a monophasic disease with severe muscle weakness, which is followed by recovery to a variable extent and duration.³ CIDP and MMN are chronic polyneuropathies requiring long-term treatment, usually with intravenous immunoglobulins (IVIg) or corticosteroids. In SARS-CoV-2 vaccination phase III trials, individuals with a prior diagnosis of GBS or receiving IVIg or systemic corticosteroids within months before study vaccine administration were excluded from participation.⁴⁻⁷ Therefore, data from these trials regarding safety of SARS-CoV-2 vaccinations cannot instantaneously be extrapolated to most of the patients with these immune-mediated neuropathies.

Concerns regarding safety of vaccination and immune-mediated neuropathies stem from a described eightfold increased incidence rate of GBS after vaccination during the H1N1 influenza vaccination campaign in 1976.^{8,9} Similar correlations have not been observed since, although temporal associations between vaccination and GBS have been reported.¹⁰⁻¹³ GBS has an estimated lifetime recurrence risk between 3.5% and 6.6%.^{12,14-17} No GBS recurrences were reported within 6 weeks after seasonal flu vaccination or after various other vaccines, such as pneumovax and Hepatitis A and B.^{17,18} The pathophysiologic mechanisms between vaccinations and the occurrence of GBS after vaccinations however remain unclear.¹⁹ Despite these more recent studies,²⁰ GBS is still listed as an adverse event of special interest in pharmacovigilance studies to ensure early detection of a potential association with any new vaccine. For CIDP and MMN, no increased incidence has been reported after any vaccination, such as seasonal flu vaccination. In a retrospective study, 3 of 65 patients with CIDP reported that they had experienced symptoms similar to a typical relapse of CIDP after receiving a vaccination.¹²

In the general population, an increased incidence of GBS in the 28 days after vaccination with ChadOx1 nCoV-19 (AstraZeneca) has been observed.²¹ After increased signals of GBS incidence in passive reporting systems, safety warnings were issued for both ChadOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson).^{22,23} However, an association between SARS-CoV-2 infection and an increased incidence of GBS has also been described, and this association was much stronger than for SARS-CoV-2 vaccinations.^{21,24} This highlights the value of

preventing SARS-CoV-2 infections, especially in patients with immune-mediated neuropathies, if SARS-CoV-2 vaccines can be safely administered in patients who have had GBS.

The scale of the SARS-CoV-2 vaccination campaigns created a unique opportunity to investigate the possible relationship between SARS-CoV-2 vaccination and the course of disease in immune-mediated neuropathies. The objective of this study was to explore the risk of recurrence of GBS or worsening of disease-related symptoms in CIDP and MMN after SARS-CoV-2 vaccination.

Methods

Setting and Participants

This study is a collaboration between 3 University Medical Centers with a research focus on immune-mediated neuropathies (Erasmus University Medical Center Rotterdam, Amsterdam University Medical Centers, and University Medical Center Utrecht) and the Dutch Patient Association for neuromuscular diseases (Spierziekten Nederland). Patients known with a prior diagnosis of GBS, CIDP, or MMN, aged 18 years or older, were considered eligible to participate. After written informed consent was obtained, we evaluated medical records to confirm the diagnosis in participants who participated through the Dutch Patient Association, to confirm any prior recurrences of GBS, and to gain insight in the course of disease of CIDP and MMN. We excluded individuals who had already received a SARS-CoV-2 vaccination or had tested positive for SARS-CoV-2 before study entry from analyses to prevent recall bias. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

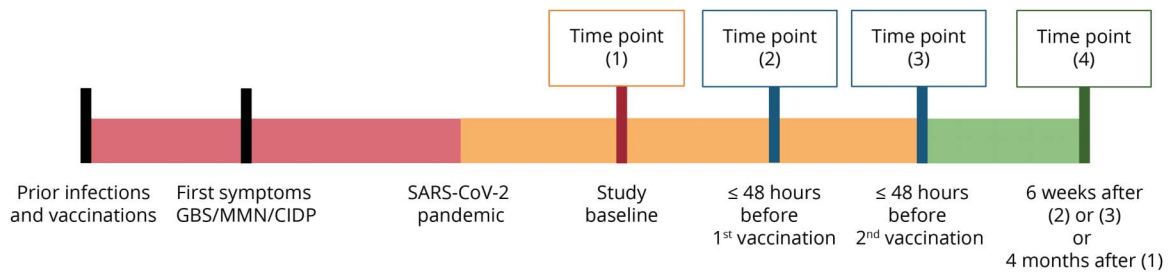
Standard Protocol Approvals, Registrations, and Patient Consents

Approval of the Medical Ethics Committee of Erasmus Medical Center in Rotterdam (MEC-2021-0103) was obtained for Erasmus University Medical Center Rotterdam and Amsterdam University Medical Centers and separately, on request, for the Medical Ethics Committee of University Medical Center Utrecht (METC-21/253). Written informed consent was obtained from all participants in the study.

Study Design

We conducted a prospective, multicenter cohort study, using disease-specific questionnaires consisting of different subsets corresponding to predefined time points. These time points are study baseline (1), within 48 hours before (each) SARS-CoV-2 vaccination (2 and 3, if applicable), and either 6 weeks

Figure 1 Study Design and Timing of Assessments



Abbreviations: GBS = Guillain-Barré syndrome, MMN = multifocal motor neuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy.

after the last SARS-CoV-2 vaccination or 4 months after baseline assessment (4), see Figure 1.

Participants who chose not to be vaccinated were asked to fill out the last subset of the questionnaire (time point 4) 4 months after completing the baseline subset (time point 1) because we estimated that the period of time between these 2 time points would then be comparable for both vaccinated and unvaccinated participants.

At baseline, participants completed items on disease history, current treatment status, and the presence of potential disease triggers, such as infections and vaccinations, within 6 weeks before the onset of the first symptoms of GBS, CIDP, or MMN. Self-reported data on demographics, current comorbidities, and use of medication were collected as well. Within 48 hours before receiving a SARS-CoV-2 vaccination (time points 2 and 3), participants completed items on current disease-related symptoms and treatment. This included items regarding disease-related symptoms such as weakness in arms or legs, sensory symptoms, fatigue, and muscle aches. In the last subset (time point 4) of the questionnaire, participants reported current disease-related symptoms, experienced changes in their disease course, and treatment alterations, as well as any SARS-CoV-2 infection since baseline (time point 1).

At time points 2 and 4, standardized questionnaires regarding disability and quality of life were included to objectively assess any changes, namely the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and the EuroQol-5D-5L (EQ-5D-5L).^{25,26}

The outcome of interest in this study was any self-reported deterioration in disease-related complaints. For GBS, deterioration was defined as any reported recurrence of GBS, initiation of immunomodulatory treatment, or hospitalization. In CIDP and MMN, disease-related complaints were defined as any reported worsening of disease-related symptoms, alteration in maintenance therapy, or hospitalization. If the reported change in disease-related symptoms consisted exclusively of fatigue and/or muscle aches, these were regarded as non-specific. A decrease of 4 or more centile points on the I-RODS between time points 2 and 4 was considered a minimal clinical

important difference.²⁷ The Paretian Classification of Health Change (PCHC) was used to summarize changes in the reported EQ-5D health status at time points 2 and 4.²⁸

Recurrences or worsening in disease-related symptoms within 6 weeks after immunization were considered as possibly causally related to SARS-CoV-2 vaccination. The time period of 6 weeks between the last vaccination (either time point 2 or 3) and the completion of the last subset (time point 4) was chosen as the increased incidence of GBS after swine flu vaccination in 1976 was described within this same period.⁹

We considered any new symptoms or worsening of existing symptoms occurring 48 hours after vaccination most likely to be a side effect of the vaccination itself and not caused by a reactivation of patients' immune-mediated neuropathy.²⁹

We contacted participants reporting a recurrence or deterioration during the course of the study for a structured phone interview and requested additional information from their treating physicians. Participants were asked about any recent infections, surgery or new concomitant diagnoses, contact with their neurologist, the rationale for any changes in therapy during follow-up, and other potentially relevant events that might have contributed to a change in experienced disease activity. In addition, patients were asked whether their symptoms had resolved and whether they would be willing to get a subsequent SARS-CoV-2 vaccine in the future. If participants stated that disease progression was present before vaccination and they did not experience sudden further deterioration after receiving a SARS-CoV-2 vaccine, we considered the worsening of symptoms unrelated.

Statistical Analysis

Statistical analyses were conducted with SPSS Statistics, version 27. Numerical variables were described using median (interquartile range) and categorical variables as absolute number (percentage). Missing values were not imputed.

Data Availability

The data supporting the findings of this study are available on reasonable request from the corresponding author. The data

are not publicly available because of privacy or ethical restrictions.

Results

Participants

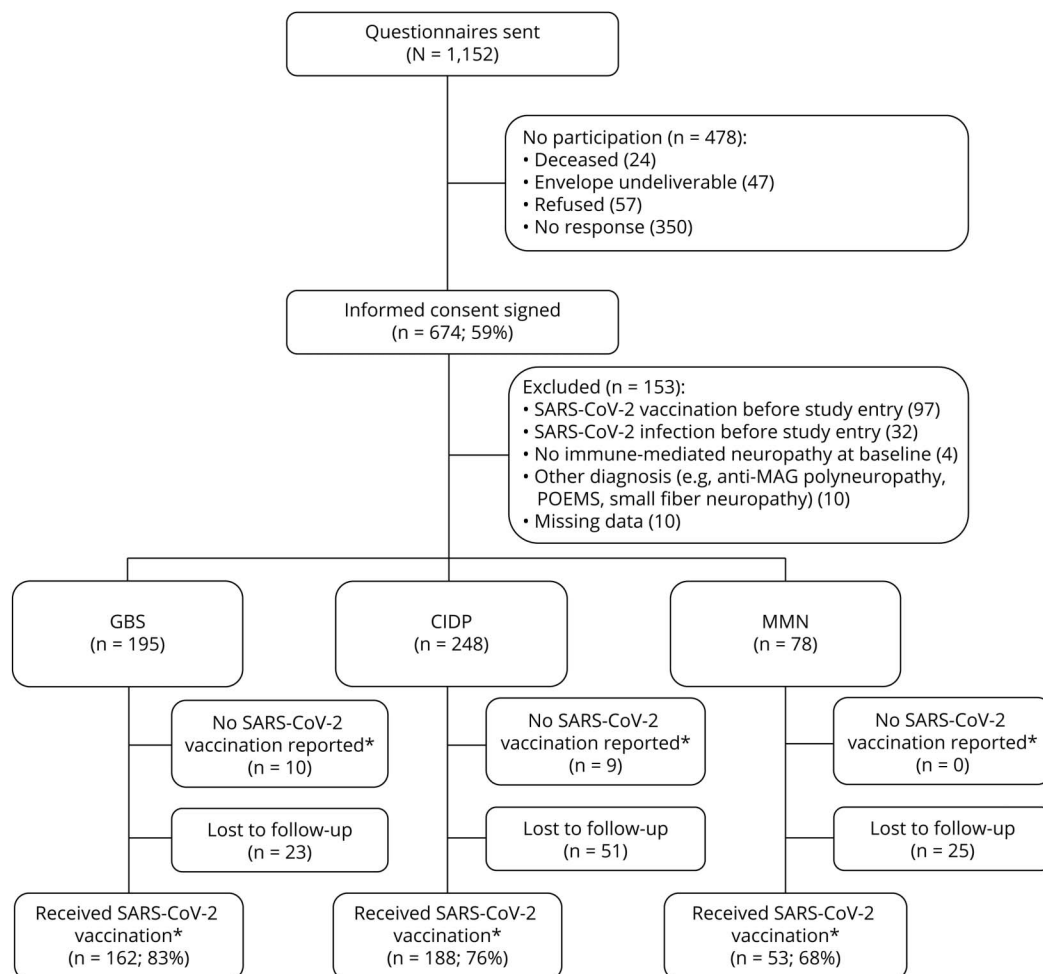
A total of 1,152 individuals were invited to participate. The 3 University Medical Centers invited 348 eligible patients with a history of GBS, 458 with CIDP, and 103 with MMN to participate. Members of the Dutch patient association for neuromuscular diseases with GBS, CIDP, or MMN were asked to contact the investigators to participate if they were eligible and interested in participating, which 243 of the 500 invited members did. Participants were included between February 20th, 2021, and August 27th, 2021. Informed consent was signed by 245 participants with a prior diagnosis of GBS, 325 participants with a prior or current diagnosis of CIDP, and 104 participants with a prior or current diagnosis of MMN, which corresponds to a response rate of 59% according to the AAPOR guideline.³⁰ A total of 478 individuals (41%) did not participate

(Figure 2). We excluded 153 participants for not having an immune-mediated neuropathy at baseline, a significant lack of data, or reporting a SARS-CoV-2 vaccination or infection before study entry. This resulted in a study cohort of 521 participants (Figure 2). We were able to verify 81% of GBS, CIDP, and MMN diagnoses by screening requested medical records for 155 participants that were included through the Dutch patient association. Of the 521 participants, 403 (77%) completed and returned the last subset after vaccination (time point 4): 162 of 195 individuals (83%) with a prior diagnosis of GBS, 188 of 248 individuals (76%) with CIDP, and 53 of 78 individuals (68%) with MMN.

Baseline Characteristics

Most of the participants were male (59%), the median age was 64 years (interquartile range, 55–72 years), and the median time since diagnosis was 9 years (interquartile range 5–18 years) (Table 1). Of the 215 participants with CIDP completing the item, 156 (73%) reported that they received maintenance treatment for their diagnosis, as did 73 of 75 participants (97%) with MMN. Maintenance treatment for

Figure 2 Flowchart of the Study Population and Response Rate



Abbreviations: GBS = Guillain-Barré syndrome, MMN = multifocal motor neuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy. *These participants completed the last questionnaire, at time point 4.

Table 1 Characteristics of All Participants With Guillain-Barré Syndrome (GBS), CIDP, and MMN

	GBS n = 195 (37)	CIDP n = 248 (48)	MMN n = 78 (15)
Male	98 (50)	150 (60)	58 (74)
Age at diagnosis	48 (34–57)	55 (47–64)	47 (40–52)
Study baseline (time point 1)			
Age	66 (54–72)	66 (57–72)	59 (52–65)
Years since diagnosis	15 (7–23)	6 (3–13)	10 (5–17)
Number of participants receiving maintenance treatment^a		156/215 (73)	73/75 (97)
IVIg		119 (76)	72 (99)
CS		26 (17)	1 (1)
Plasmapheresis		11 (7)	
Number of participants willing to vaccinate (%)	145/187 (78)	211/237 (89)	65/78 (83)
Uncertain	31 (17)	22 (9)	12 (15)
Unwilling	11 (6)	4 (2)	1 (1)

Abbreviations: GBS = Guillain-Barré syndrome, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy. IVIg = intravenous immunoglobulins, CS = corticosteroids.

Data are formatted as absolute number (%) or median (interquartile range).
^a Not including participants in whom treatment was discontinued before study baseline.

CIDP consisted of immunoglobulins in 119 participants (76%; 109 intravenous, 7 subcutaneous), corticosteroids in 26 (17%), and plasmapheresis in 11 participants (7%). A recurrence of GBS before study entry was reported by 15 participants. Ten recurrences could be confirmed, and the other 5 were not considered recurrences after critically reviewing the medical records.

Symptoms of infection in the 6 weeks before the onset of neurologic symptoms were reported by 125 of 194 participants (64%) with GBS, most often gastrointestinal symptoms. For CIDP, 54 of 177 participants (31%) reported preceding infectious symptoms, most often flu.

Nine participants with GBS and 10 with CIDP reported a vaccination in the 6 weeks before the onset of their neurologic symptoms. More specifically, 5 of the participants with GBS and 5 with CIDP reported a flu vaccination. Two participants with CIDP and 1 with GBS reported a hepatitis vaccination. Other vaccinations reported before GBS were pneumococcal, meningococcal, and typhoid vaccination. One CIDP participant reported a combined pneumococcal and flu vaccination before onset of neurologic symptoms. Of all participants, 37 (7%) reported that they had been advised against any particular vaccination in the past by their physician, and 81 (16%) were either uncertain or unwilling to

get a SARS-CoV-2 vaccination. Most often, participants reported uncertainty on the safety of the vaccine regarding their diagnosis of immune-mediated neuropathy as the reason for their hesitancy.

Course of Disease After SARS-CoV-2 Vaccination

In total, 465 participants received 844 vaccinations during the course of this study. Most participants, 302 (65%) received at least 1 BNT162b2 (Pfizer/BioNTech) vaccine, 69 (15%) a ChadOx1 nCoV-19 (AstraZeneca), 36 (8%) mRNA-1273 (Moderna), and 12 (3%) Ad26.COVS.2.S (Jansen/Johnson&Johnson). Nineteen participants (4%) did not obtain a SARS-CoV-2 vaccination during study follow-up. One of these participants with CIDP reported worsening of weakness, sensory symptoms, and fatigue, resulting in a change in maintenance treatment. At time point 4, 6 participants reported that they had received a positive SARS-CoV-2 PCR test result since study commencement.

There were no recurrences of GBS after SARS-CoV-2 vaccination. One of 162 participants with a prior diagnosis of GBS did report a recurrence of symptoms after SARS-CoV-2 vaccination, which resulted in hospital admission. However, after critically reviewing the medical records, it seemed that the symptoms and signs were due to lumbar spinal stenosis, for which the patient underwent decompressive surgery, resulting in resolution of symptoms. Therefore, this case was not considered as a recurrence of GBS. Of the 27 participants contacted for having not completed the final questionnaire, 17 confirmed that they had not experienced a recurrence of GBS and were included in the analysis; 10 participants did not reply.

Ten of 188 participants (5%) with CIDP reported a worsening in disease-related symptoms after SARS-CoV-2 vaccination, such as weakness and/or sensory disturbances (Table 2). However, none contacted their neurologist for an unscheduled evaluation for these symptoms (Table 2). Five of these 10 participants did report an alteration in their treatment regimen. In all except one of the patients who was able to estimate the time to normalization of symptoms, the symptoms resolved within 4 weeks. In 1 patient, it took 8 weeks. Three of the 10 participants had a deterioration corresponding to minimal clinical important difference on the I-RODS at time point 4. All the 10 participants stated they would obtain a booster vaccination when available.

For MMN, a worsening of disease-related symptoms was reported by 2 of 53 (4%) participants (time point 4). One patient received additional treatment with IVIg 6 weeks after vaccination, where after the symptoms resolved.

Discussion

Key Results

No increased risk of recurrence of GBS after SARS-CoV-2 vaccination was found in this study. A small number of

Table 2 Patient-Reported Worsening of Disease-Related Symptoms in Patients With CIDP and MMN ≤ 6 Weeks After SARS-CoV-2 Vaccination

	1	2	3	4	5	6	7	8	9	10	11	12
	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	MMN	MMN
BASELINE (TIME POINT 1)												
Sex	M	M	F	M	F	M	F	F	M	M	F	F
Age	51	54	55	65	66	66	69	70	74	82	63	73
Maintenance treatment	IVIg	IVIg	None	CS	IVIg	Trial	IVIg	IVIg	IVIg	IVIg	IVIg	IVIg
Fluctuating course of disease, ongoing from before vaccination^a	+	+	+	+	+	-	+	+	-	+	+	-
AFTER VACCINATION (TIME POINT 4)												
Vaccine brand	P	P	M	AZ	P	P	P	P	P	P	AZ	P
Temporal association to first or second vaccination	1	2	2	1	1	2	2	2	2	2	1	n/a
Time to onset of symptoms	>14 d	8–14 d	3–7 d	8–14 d	8–14 d	>14 d	8–14 d	>14 d	8–14 d	n/a	>14 d	n/a
Reported change in symptoms	WA, SS, F, MA	W-NOS	WL, SS, F, MA	WA, SS	WA, WL, SS, F	SS, F	WA, WL, SS, F	SS, F	WA, WL, SS	WL, SS, F, MA	WA, WL, F, MA	WL, F
Participant actively contacted neurologist (requested an unscheduled visit)	-	-	-	-	-	-	-	-	-	-	+	-
Other concurrent event/relevant diagnosis	-	-	Recurring pneumonia	Tapering treatment	Viral infection, hypokalemia (medication induced)	-	-	-	-	n/a	-	-
Treatment alteration at next visit	Increase dose, interval shortened	-	-	Scheduled tapering postponed	Double dose of IVIg, once	-	Increase dose, shorter interval	-	-	Increase dose IVIg/ start CS	Extra course of IVIg	-
Worsening of symptoms resolved?	+	n/a	+	+	+	+	+	-	+	-	+	+
I-RODS: MCID deterioration^b	n/a	-	-	+	-	+	+	-	-	n/a	n/a	n/a

Continued

Table 2 Patient-Reported Worsening of Disease-Related Symptoms in Patients With CIDP and MMN ≤6 Weeks After SARS-CoV-2 Vaccination (continued)

	1	2	3	4	5	6	7	8	9	10	11	12
	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	CIDP	MMN	MMN
Change EQ-5D-5L^c	Unknown	Mixed	Improved	Mixed	Worse	No change	Worse	Unknown	No change	No change	Worse	Improved
Interpretation	EOD, progressive from before vaccination	Fluctuating course of disease, ongoing from before vaccination	Fluctuating course of disease, other possible cause	Other possible cause	Other possible cause	No other explanation found	Progressive from before vaccination	Possible EOD effect	No other explanation found	Fluctuating course of disease ongoing from before vaccination	Increasing IVIg requirement, ongoing from before vaccination	Slow disease progression (MMN)

Abbreviations: AZ = AstraZeneca; CIDP = chronic inflammatory demyelinating polyneuropathy; CS = corticosteroids; EOD = end-of-dose; F = fatigue; MMN = multifocal motor neuropathy; IVIg = intravenous immunoglobulins; M = Moderna; MA = muscle aches; MCID = minimal clinical important difference; n/a = not available; NOS = not otherwise specified; P = Pfizer/BioNTech; SS = sensory symptoms; WA = weakness arms; WL = weakness legs.
^a These participants reported the presence of end-of-dose symptoms or changing presence and severity of disease-related symptoms before SARS-CoV-2 vaccination.
^b A minimal clinical important difference (MCID) on the I-RQDS scale is defined as a deterioration of at least 4 points on the centile scale.
^c Change EQ-5D-5L: worsening = deterioration on at least 1 of 5 items; improvement = improvement on at least 1 of 5 items; mixed = both deterioration and improvement on at least 1 of 5 items.

participants with CIDP and MMN reported that they had experienced a worsening of disease-related symptoms during the study period. Most of these participants reported having a fluctuating course of disease before SARS-CoV-2 vaccination. Other possible explanations for disease fluctuations, such as concurrent infections or a recent tapering attempt of maintenance treatment, were reported as well. Although changes to maintenance treatment regimens were made in 6 participants, the worsening of symptoms was self-limited in most participants. None required a restart of treatment.

Interpretation

One retrospective cohort study evaluated the risk of recurrence of GBS after vaccination with BNT162b2 (Pfizer/BioNTech) using the registrations of all hospital visits of 702 patients previously diagnosed with GBS.³¹ A recurrence of GBS after the second dose of BNT162b2 (Pfizer/BioNTech) vaccine was found in only 1 patient.³¹ By contrast, we conducted a prospective population-based cohort study. The study design allowed for comparison before and after exposure to any SARS-CoV-2 vaccine. We were able to further estimate the impact on the course of disease in all participants independent of whether they sought help from a hospital-based physician.

Various case reports on the temporal association between incident cases of GBS and SARS-CoV-2 vaccination have been published since the commencement of national vaccination programs.³²⁻³⁴ However, a study describing an incident case of GBS in both the intervention and placebo arm in the phase II trial for the Ad26.COVS (Janssen/Johnson & Johnson) vaccine illustrates that a temporal association is not necessarily indicative of a causal association.³⁵ A recent study showed an increased incidence rate ratio for GBS after vaccination with the ChadOx1 nCoV-19 (AstraZeneca) vaccine, although the incidence rate ratio after a positive SARS-CoV-2 PCR test was larger.²¹ An excess GBS risk of 0.576 per 100,000 administered doses of ChadOx1 nCoV-19 (AstraZeneca) was also found in a nationwide observational study.³⁶ Another study found no association between the administration of 11,845,128 doses of BNT162b2 (Pfizer/BioNTech) vaccinations and incident cases GBS in the following 6 weeks.³⁷

There are no studies describing the safety of SARS-CoV-2 vaccinations in patients with either CIDP or MMN. However, our results are similar to studies on the safety of the BNT162b2 (Pfizer/BioNTech) vaccine in patients with multiple sclerosis.³⁸ Asking patients about experienced adverse effects after exposure to vaccinations might induce a placebo effect.³⁹ A negative attitude toward vaccination might lead participants to overreport a change in disease-related symptoms. Therefore, detailed data on the severity of symptoms, whether symptoms had resolved, and their attitude toward subsequent SARS-CoV-2 vaccinations were obtained by contacting participants. We also contacted their treating neurologist, with permission of the participants, to verify the severity of the change in symptoms. Our study indicated that, despite several reports of a change in disease-related symptoms, most participants concluded that

these changes were temporary and still had a positive attitude toward SARS-CoV-2 vaccinations. Spontaneous disease fluctuations cannot be excluded because these are frequently seen in CIDP, with 1 study reporting disease fluctuations in 52% of patients with CIDP.⁴⁰

Limitations

Our study has several limitations. First, patients with either residual symptoms or active disease may have been more inclined to participate, introducing selection bias. By contrast, individuals without any current disease-related symptoms might have been less inclined to participate, while also being potentially at risk for disease recurrence or exacerbation. Overrepresentation of more severely affected patients might have resulted in an overestimation of the impact of SARS-CoV-2 vaccination on the course of disease. Most of the participants with CIDP or MMN reporting a worsening of their disease-related symptoms also reported having a fluctuating course of disease before SARS-CoV-2 vaccination. This might have resulted in an overestimation of the effect of SARS-CoV-2 vaccination on the course of disease. Second, participants may have underreported disease-related symptoms that had already resolved or which they considered unrelated. Third, most of the participants received a vaccination with BNT162b2 (Pfizer/BioNTech). Only 23 participants with a history of GBS received a ChadOx1 nCoV-19 (AstraZeneca), and 12 participants in total received Ad26.COV2.S (Janssen/Johnson&Johnson). These subgroups are too small to draw any conclusions. Finally, this study is mainly based on patient-reported data. Medical records to verify the diagnosis could not be obtained for all participants. However, we verified patient reports by additional phone interviews and by evaluating data supplied by treating physicians. An important limitation in the reported worsening in disease course is the lack of objective confirmation, either by using grip strength measurement tools or by treating neurologists, which might have resulted in an overestimation. Not all participants completed the last subset of the questionnaire (time point 4), and not all these participants responded to attempts to seek contact. Therefore, we cannot rule out that these participants had a recurrence of GBS.

This study indicates no increased risk for recurrence of GBS or severe disease exacerbations in CIDP and MMN after SARS-CoV-2 vaccination. The reported worsening of disease-related symptoms after SARS-CoV-2 vaccination was mild and did not require treatment alteration in most participants. Symptoms resolved within several weeks in most participants, and none required hospitalization.

Study Funding

This study was supported by Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Disclosure

A.E. Baars reports no disclosures; Dr K. Kuitwaard received a research grant from Takeda and a consultancy fee from Takeda paid to the institution outside the submitted work.

She received a speakers fee from Grifols paid to the institution outside the submitted work; L.C. de Koning reports no disclosures; L.W.G. Luijten reports no disclosures; W.M. Kok reports no disclosures; Dr F. Eftimov report grants from ZonMw (Dutch governmental agency) to study vaccination responses in patients with autoimmune diseases. Outside of the submitted work, as principal investigator of INCbase, he also reports investigator-initiated grants from Kedrion, Terumo BCT, CSL-Behring, Grifols and Takeda Pharmaceutical Company, and grants from ZonMw and Prinses Beatrix Spierfonds (a Dutch charity) for studies in CIDP. In addition, his institution has received fees from UCB Pharma, CSL Behring, Grifols, and Takeda for advisory board membership and/or lectures. All grants and fees were paid to his institution. He is a member of the Cochrane Neuromuscular Editorial Board; Dr L. Wieske received research grants from Grifols (2019) and the GBS/CIDP Foundation (2020) for the study of disease activity biomarkers in CIDP; Dr H.S. Goedee received research grants from Prinses Beatrix Spierfonds and travel grant/speaker fee from Shire/Takeda; Dr W.L. van der Pol has provided ad hoc consultancy services (scientific advisory board) to Biogen, Roche, Novartis Gene Therapies, Avexis, and Takeda and has obtained grants from Vriendenloterij, Spieren voor Spieren, and Prinses Beatrix Fonds; P.H. Blomkwist-Markens reports no disclosures; A.M.C. Horemans reports no disclosures; Dr B.C. Jacobs received research grants for work outside the current study from Baxalta, Grifols, CSL-Behring, Annexon, Hansa Biopharma, Roche, Prinses Beatrix Spierfonds, GBS-CIDP Foundation International, and Horizon 2020, and consultancy fees from Roche for activities outside the current study. All grants and fees were paid to his institution. He is the chair of the Steering Committee of International GBS Outcome Study (IGOS); Dr P.A. van Doorn received research grants from Prinses Beatrix Spierfonds, The Netherlands Organisation for Health Research and Development (ZonMW), Sanquin Blood supply, Takeda, and Grifols. He is a member of Scientific Advisory Committee/Steering Committee Trials for Annexon, Argenx, Hansa, Octapharma, Sanofi, and Roche. All grants and fees were paid to his institution. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* April 13, 2022. Accepted in final form August 23, 2022. Submitted and externally peer reviewed. The handling editor was Anthony Amato, MD, FAAN.

Appendix Authors

Name	Location	Contribution
Adája E. Baars, MD	Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
Krista Kuitwaard, MD, PhD	Department of Neurology, Erasmus MC University Medical Center, Rotterdam; Department of Neurology, Albert Schweitzer Hospital, Dordrecht, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Laura C. de Koning, BSc	Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Linda W.G. Luijten, MD	Department of Neurology, Erasmus MC University Medical Center, Rotterdam; St. Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
W. Maaike Kok, BSc	Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Filip Eftimov, MD, PhD	Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Luuk Wieske, MD, PhD	Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
H. Stephan Goedee, MD, PhD	Department of Neurology and Neurosurgery, Brain Center University Medical Center Utrecht, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
W. Ludo van der Pol, MD, PhD	Department of Neurology and Neurosurgery, Brain Center University Medical Center Utrecht, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Patricia H. Blomkwist-Markens	Dutch Patient Organization for Neuromuscular Diseases, Baarn, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Anja M.C. Horemans, MD, PhD	Dutch Patient Organization for Neuromuscular Diseases, Baarn, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Bart C. Jacobs, MD, PhD	Department of Neurology, Erasmus MC University Medical Center; Department of Immunology, Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Pieter A. van Doorn, MD, PhD	Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

References

- Bourdette D, Killestein J. Quelling public fears about Guillain-Barré syndrome and COVID-19 vaccination. *Neurology*. 2021;96(22):1021-1022. doi: 10.1212/WNL.00000000000011882
- Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. *Brain*. 2021;144(2):357-360. doi: 10.1093/brain/awaa444
- Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol*. 2019;15(11):671-683. doi: 10.1038/s41582-019-0250-9
- Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. *N Engl J Med*. 2021;384(23):2187-2201. doi: 10.1056/NEJMoa2101544
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi: 10.1056/NEJMoa2034577
- Voysey M, Clemens SAC, Madhi SA. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111. doi: 10.1016/S0140-6736(20)32661-1
- Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. doi: 10.1056/NEJMoa2035389
- Sejvar JJ, Pfeifer D, Schonberger LB. Guillain-barré syndrome following influenza vaccination: causal or coincidental?. *Curr Infect Dis Rep*. 2011;13(4):387-398. doi: 10.1007/s11908-011-0194-8
- Schonberger LB, Bregman DJ, Sullivanbolyai JZ, et al. Guillain-barré-syndrome following vaccination in the national influenza immunization program, united-states, 1976-1977. *Am J Epidemiol*. 1979;110(2):105-123. doi: 10.1093/oxfordjournals.aje.a112795
- Vellozzi C, Iqbal S, Broder K. Guillain-barré syndrome, influenza, and influenza vaccination: the epidemiologic evidence. *Clin Infect Dis*. 2014;58(8):1149-1155. doi: 10.1093/cid/ciu005
- Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. *Drug Saf*. 2009;32(4):309-323. doi: 10.2165/0002018-200932040-00005
- Pritchard J, Mukherjee R, Hughes RAC. Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. *J Neurol Neurosurg Psychiatry*. 2002;73(3):348-349. doi: 10.1136/jnnp.73.3.348
- Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom general practice research database. *Am J Epidemiol*. 2009;169(3):382-388. doi: 10.1093/aje/kwn310
- Ishii J, Yuki N, Kawamoto M, Yoshimura H, Kusunoki S, Kohara N. Recurrent Guillain-Barré syndrome, Miller Fisher syndrome and Bickerstaff brainstem encephalitis. *J Neurol Sci*. 2016;364:59-64. doi: 10.1016/j.jns.2016.03.008
- Kuitwaard K, van Koningsveld R, Ruts L, Jacobs BC, van Doorn PA. Recurrent Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry*. 2009;80(1):56-59. doi: 10.1136/jnnp.2008.156463

16. Mossberg N, Nordin M, Movitz C, et al. The recurrent Guillain-Barré syndrome: a long-term population-based study. *Acta Neurol Scand*. 2012;126(3):154-161. doi: 10.1111/j.1600-0404.2012.01667.x
17. Baxter R, Lewis N, Bakshi N, et al. Recurrent Guillain-Barré syndrome following vaccination. *Clin Infect Dis*. 2012;54(6):800-804. doi: 10.1093/cid/cir960
18. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst*. 2009; 14(4):310-315. doi: 10.1111/j.1529-8027.2009.00243.x
19. Goedee HS, Attarian S, Kuntzer T, Van den Bergh P, Rajabally YA. Iatrogenic immune-mediated neuropathies: diagnostic, epidemiological and mechanistic uncertainties for causality and implications for clinical practice. *J Neurol Neurosurg Psychiatry*. 2021;92(9):975-982. doi: 10.1136/jnnp-2019-321663
20. SO2-D2 SPEAC. 1.2 Priority List of COVID-19 Adverse Events of Special Interest: Quarterly Update December 2020; 2020. Accessed September 15, 2021. brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf.
21. Patone M, Handunnetthi L, Saatci D, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. *Nat Med*. 2021;27(12): 2144-2153. doi: 10.1038/s41591-021-01556-7
22. Meeting EMA. Highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 July 2021. Updated July 5, 2021. Accessed March 30, 2022. ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-july-2021.
23. Woo EJ, Mba-Jonas A, Dimova RB, Alimchandani M, Zinderman CE, Nair N. Association of receipt of the Ad26.COV2.S COVID-19 vaccine with presumptive Guillain-Barré syndrome. *JAMA*. 2021;326(16):1606-1613. doi: 10.1001/jama.2021.16496
24. Luijten LWG, Leonhard SE, van der Eijk AA, et al. Guillain-Barré syndrome after SARS-CoV-2 infection in an international prospective cohort study. *Brain*. 2021; 144(11):3392-3404. doi: 10.1093/brain/awab279
25. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall disability scale (RODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76(4): 337-345. doi: 10.1212/WNL.0b013e318208824b
26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-SL). *Qual Life Res*. 2011;20(10):1727-1736. doi: 10.1007/s11136-011-9903-x
27. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force-Second revision. *J Peripher Nerv Syst*. 2021;26(3):242-268. doi: 10.1111/jns.12455
28. Devlin N, Parkin D, Janssen B. *Methods for Analysing and Reporting EQ-5D Data*, 1st ed. Springer Cham; 2020:29-34. doi: 10.1007/978-3-030-47622-9
29. Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis*. 2021;21(7):939-949. doi: 10.1016/S1473-3099(21)00224-3
30. The American Association for Public Opinion Research. *Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys*, 9th ed. AAPOR; 2016.
31. Shapiro Ben David S, Potasman I, Rahamim-Cohen D. Rate of recurrent Guillain-Barré syndrome after mRNA COVID-19 vaccine BNT162b2. *JAMA Neurol*. 2021; 78(11):1409-1411. doi: 10.1001/jamaneurol.2021.3287
32. Allen CM, Ramsamy S, Tarr AW, et al. Guillain-barré syndrome variant occurring after SARS-CoV-2 vaccination. *Ann Neurol*. 2021;90(2):315-318. doi: 10.1002/ana.26144
33. Maramattom BV, Krishnan P, Paul R, et al. Guillain-barré syndrome following ChAdOx1-S/nCoV-19 vaccine. *Ann Neurol*. 2021;90(2):312-314. doi: 10.1002/ana.26143
34. Razok A, Shams A, Almeer A, Zahid M. Post-COVID-19 vaccine Guillain-Barré syndrome; first reported case from Qatar. *Ann Med Surg (Lond)*. 2021;67:102540. doi: 10.1016/j.amsu.2021.102540
35. Márquez Loza AM, Holroyd KB, Johnson SA, Pilgrim DM, Amato AA. Guillain-Barré syndrome in the placebo and active arms of a COVID-19 vaccine clinical trial: temporal associations do not imply causality. *Neurology*. 2021;96(22):1052-1054. doi: 10.1212/WNL.00000000000011881
36. Keh RYS, Scanlon S, Datta-Nemdharry P, et al. COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National Immunoglobulin Database. *Brain*. 2022. doi: 10.1093/brain/awac067
37. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326(14):1390-1399. doi: 10.1001/jama.2021.15072
38. Lotan I, Wilf-Yarkoni A, Friedman Y, Stiebel-Kalish H, Steiner I, Hellmann MA. Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis (MS): early experience from a tertiary MS center in Israel. *Eur J Neurol*. 2021;28(11):3742-3748. doi: 10.1111/ene.15028
39. Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: a systematic review. *Lancet Reg Health Eur*. 2022;12:100253. doi: 10.1016/j.lanepe.2021.100253
40. Allen JA, Pasnoor M, Dimachkie MM, et al. Quantifying treatment-related fluctuations in CIDP: results of the GRIPPER study. *Neurology* 2021;96(14):e1876-e1886. doi: 10.1212/WNL.00000000000011703

Neurology®

SARS-CoV-2 Vaccination Safety in Guillain-Barré Syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, and Multifocal Motor Neuropathy

Adája E. Baars, Krista Kuitwaard, Laura C. de Koning, et al.

Neurology 2023;100:e182-e191 Published Online before print September 20, 2022

DOI 10.1212/WNL.0000000000201376

This information is current as of September 20, 2022

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/100/2/e182.full
References	This article cites 37 articles, 7 of which you can access for free at: http://n.neurology.org/content/100/2/e182.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/100/2/e182.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Chronic inflammatory demyelinating polyneuropathy http://n.neurology.org/cgi/collection/chronic_inflammatory_demyelinating_polyneuropathy Cohort studies http://n.neurology.org/cgi/collection/cohort_studies COVID-19 http://n.neurology.org/cgi/collection/covid_19 Guillain-Barre syndrome http://n.neurology.org/cgi/collection/guillainbarre_syndrome
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

